

## **REMARKS**

### **I. Status of Claims and Formal Matters**

Claims 1-35 are pending in the application. By entry of this amendment, claims 1-10, 12-15 and 21 are cancelled and claims 11, 16, 17 – 20, 22 – 26, 28 – 33 are amended herein to more clearly define the claimed subject matter.

### **II. The Rejections Under 35 U.S.C. § 112 Are Overcome**

Claims 16-20, 22-26 and 28-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully disagree and traverse this rejection.

The Examiner points out that the claims do not clearly define the dose that is to be administered to the subject because it is only listed as a percent. The Examiner correctly interpreted claims 16-20, 22-26 and 28-32 to refer to the percent of active agent in the pharmaceutical composition. Claims 16-20, 22-26 and 28-32 have been amended in accord with the Examiner's understanding, and now more clearly recite the dose to be administered in the claimed methods.

In view of the foregoing, reconsideration and withdrawal of all rejections under 35 U.S.C. § 112 are respectfully requested.

### **III. The Rejections Under 35 U.S.C. § 103 Are Overcome**

Claims 11-13, 16-26 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Elkhoury et al (USPN 5589480) in view of Ptchelintsev et al. (USPN 5834513). Applicants respectfully disagree and traverse this rejection.

By entry of this amendment, the present invention is directed to methods for providing synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject. The combined administration of morphine and butamben for providing topical analgesia is alleged to have been prima facie obvious to one of ordinary skill in the art at the time of filing because the combination of Elkhoury, which teaches the use of morphine for providing topical analgesia, with Ptchelintsev, which teaches the use of butamben as a topical analgesic,

would have been logical given that their analgesic properties were each known individually in the art.

It is respectfully submitted that the combination of morphine and butamben in the periphery produced a synergistic result that would have been unexpected to one of skill in the art of pain management at the time that the present application was filed. Further details of this result are provided by the attached Declaration of the Inventors under 37 C.F.R. § 1.132 (“the Declaration”). The Declaration describes the results as published in the scientific journal *Anesthesia and Analgesia (Analgesic Synergy Between Topical Morphine and Butamben in Mice* Vol. 97:4, 2003). As stated in the Declaration, the methods described in the publication were conducted according to the teachings of the present application, and in particular, as described in the Examples. The publication further describes the production of synergistic analgesia in the periphery of a mammalian subject resulting from the application of a topical butamben and morphine combination. Methods of the invention provide a particular advantage to the skilled practitioner by enabling a potent, non-systemic treatment of peripheral pain.

According to M.P.E.P. 716.01(a) “[a]ffidavits or declarations containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. § 103(a). Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating “synergism”). See *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804 (Fed. Cir. 1989), *cert. denied*, 493 U.S. 975 (1989); see also *In re Corkill*, 711 F.2d 1496 (Fed. Cir. 1985) (Stating that “[a] greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue.”). Therefore, the Declaration, taken together with the teachings of synergism between opioid analgesics and local anesthetics in the present application, amounts to at least probative and persuasive evidence of non-obviousness. Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103 are respectfully requested for claims 11-13, 16-26, and 33.

Claims 27-32 are rejected under 35 U.S.C. § 103 as being unpatentable over Elkhoury et al. and Ptchelintsev as applied to claims 11-13, 16-26, and 33 above, and further in view of Mayer et al. (USPN 5,840,731) Claims 34-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Elkhoury et al. and Ptchelintsev as applied to claims 11-13, 16-26, and 33

above, and further in view of Soo et al. (USPN 5,028,595). Applicants respectfully disagree and traverse these rejections.

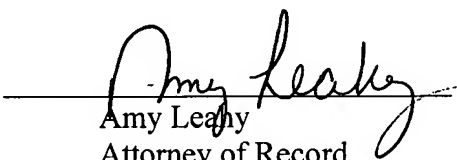
By entry of this amendment, the pending claims are directed to methods for providing synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject. Evidence in support of the unexpected synergism between morphine and butamben in the periphery is submitted herewith and therefore, as discussed in detail above, claims 11-13, 16-26, and 33 are nonobvious in view of the combination of cited references. Claims 27-32 and 34-35 ultimately depend from claim 11. If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Moreover, the further combination of either Mayer et al. or Soo et al. with the combination of Elkhoury et al. and Ptchelintsev fails to teach or suggest synergism between morphine and butamben in the periphery. Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103 are respectfully requested for claims 27-32 and 34-35.

**CONCLUSION**

In view of the amendments and remarks herewith, the application is in condition for allowance. Favorable reconsideration of the application, reconsideration, and withdrawal of the objections to and rejections of the application, and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

Respectfully submitted,

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